Influence of the cold challenge on the discriminatory capacity of the digital distal-dorsal difference in the thermographic assessment of Raynaud's phenomenon

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Abstract

Objectives. To investigate the influence of a standardised cold stress test (CST) on the thermographic 'distal-dorsal difference' (DDD) and its capacity to differentiate between disease states in the assessment of Raynaud's phenomenon (RP), and to compare the discriminatory capacity of the DDD of individual digits with composite indices of multiple digits.

Methods. Thermographic images of 55 patients with primary RP (PRP, n=27) and systemic sclerosis (SSc, n=28) who had undergone assessment of RP were retrospectively reviewed. The DDD for individual digits, and composite scores of multiple digits, were calculated at baseline (23°C), and 10 minutes following CST. The discriminatory capacity of the mean DDD, and the proportion of patients with a clinically meaningful DDD of <-1°C, were assessed for individual digits and composite indices, at baseline and following cold challenge.

Results. There was a more pronounced decrease of the DDD (indicating reduced distal perfusion) following CST in patients with PRP compared to SSc. The disparity in response to CST between groups narrowed the differences that were present at baseline, reducing the discriminatory capacity of the DDD for all endpoints. Sparing of the thumbs occurs to a greater extent in SSc ($P<0.005$) compared with PRP ($P<0.05$) but does not facilitate differentiation between groups. Large variability of the DDD within groups precludes easy differentiation between disease states. Composite indices of multiple digits are preferable to individual digital assessment.

Conclusions. The discriminatory capacity of the DDD is lost following CST. The CST may not be essential in the thermographic assessment of RP, potentially allowing greater use of thermography in clinical practice.

Introduction

Raynaud's phenomenon (RP) describes episodic abnormal digital vasoconstriction following cold exposure or emotional distress (Wigley, 2002). Primary RP (PRP) is common, has no systemic features and, whilst intrusive, is considered relatively benign. The term secondary RP (SRP) is reserved for conditions associated with RP. Systemic sclerosis (SSc) is a multisystem disease of unknown origin characterised by severe vasculopathy and fibrosis (LeRoy et al., 1988). RP is typically the first manifestation of SSc and vascular dysfunction tends to be more profound than in PRP, with the potential for critical ischaemia of the digits (Eisenberg, 2008; Wigley, 2002). Due to the episodic nature of RP, it is not always possible to identify clinical evidence of RP. Patient questionnaires have been developed but carry the inherent problems associated with self-report (Brennan et al., 1993). For this reason, non-invasive microvascular imaging tools are recommended for the assessment of RP and SSc to obtain objective evidence of vascular dysfunction (LeRoy and Medsger, 1992; LeRoy and Medsger, 2001). The major challenge facing clinicians is the early identification of those patients with RP at risk of developing conditions such as SSc (Clark et al., 1999).

Infrared thermography (IRT) has been used for over 30 years for the assessment of RP. Many thermographic protocols developed for the assessment of RP incorporate a local cold stress test (CST) in an attempt to recreate the environmental conditions necessary for an attack of RP *in vivo*. Several thermographic parameters, including those generated from the characteristics of the re-warming curve following cold challenge, have been successfully applied to differentiating between healthy controls and RP (Cherkas et al., 2003; O'Reilly et al., 1992; Ring, 1980; Ring, 1990; Ring, 1988; Schuhfried et al., 2000). Recent attention has been directed to those parameters capable of successfully discriminating between primary and secondary RP. The magnitude of the longitudinal thermal gradient (the 'distal-dorsal difference, DDD) within the digits of subjects with RP is one such parameter that can differentiate between disease states and may be superior

to those parameters generated from re-warming curve characteristics (Anderson et al., 2007; Clark et al., 1999).

Descriptions of RP typically refer to recurrent episodes of discolouration and pain affecting the fingers and toes. Other sites that may be affected include the nose, ears, tongue and nipples, however the thumbs are thought to remain relatively spared (Coffman, 1991). Recent studies have confirmed this both clinically and thermographically, whilst also identifying potential additional prognostic importance of involvement of the thumb (Chikura et al., 2010; Chikura et al., 2008). To date, no studies have evaluated the influence of a standardised cold challenge on the DDD and its capacity to differentiate between disease states. Furthermore, no studies have compared the discriminatory capacity of the DDD of individual digits (including the thumbs) with composite indices of multiple digits. In the present study, we have addressed these issues by undertaking a retrospective review of thermal images from unselected patients in whom thermographic assessment of RP, incorporating a standardised cold challenge, had been undertaken.

Methods

Subjects

Patients were identified retrospectively from our connective tissue disease database on the basis that they had undergone thermographic assessment between 2001 and 2011, and had documented evidence of Raynaud's requiring at least one colour change; white, blue or red of the digits in response to cold exposure (Brennan et al., 1993). Case notes were reviewed and patients categorised according to proposed criteria for PRP (LeRoy and Medsger, 1992) and SSc (LeRoy and Medsger, 2001) without prior knowledge of thermographic results. All subjects provided informed written consent and the study had prior approval from the Bath Research Ethics Committee.

Thermal imaging protocol

All patients assessed underwent the same RP protocol, under standardised conditions. Images were captured using the same Thermovision camera (FLIR systems, Danderyd, Sweden) and processed using the commercially available CTHERM software (Version 2.3, University of Glamorgan). All subjects were asked to avoid caffeine, alcohol, smoking and strenuous exercise for 4 hours prior to assessment. Baseline images of the dorsum of both hands were taken following acclimatisation at 23°C (+/- 0.5°C) for 15 minutes. Patients then submerged their gloved hands (to avoid subsequent evaporative cooling) in a water bath at 20°C (+/- 0.1°C) for a period of 60s. Repeat thermographic images were obtained 10 minutes following cold challenge.

Image analysis

The distal-dorsal difference was calculated and analysed as previously described (Anderson et al., 2007; Chikura et al., 2010). Briefly, the temperature of the dorsum of the hand was subtracted from a region between the nailfold and distal interphalangeal joint of the corresponding digits (including thumbs) for each hand (see figure 1A). A negative gradient would therefore indicate cooler fingertips. The lower (i.e. worse) score for each finger (right *vs*. left) was considered for subsequent analysis of individual digits as previously described (Chikura et al., 2010; Chikura et al., 2008). In accordance with previous work, a DDD of <-1°C was considered clinically meaningful (Chikura et al., 2010; Clark et al., 1999). DDDs for each digit were calculated at baseline and 10 minutes following cold challenge. The mean of lowest DDD, and the proportion of patients with a clinically meaningful DDD of <-1°C, was calculated for individual digits. Composite indices were calculated before and after cold challenge for each group, and included a mean of the lowest DDD of all five digits, the mean lowest DDD of the four fingers (minus thumbs), the mean maximum DDD across all fingers of both hands, and the number of patients with any fingers with a DDD of <-1°C.

Sample size

It was calculated that a minimum sample size of 17 patients per group would allow detection of a difference of 1 SD in the mean DDD between groups with a power of 80%.

Statistical analysis

The results were analysed using independent samples t tests and chi-square analysis were appropriate. Analyses were undertaken using SPSS version 17.0. All tests were 2-tailed and a *P* value of <0.05 was considered significant.

Results

Patients

Assessments from fifty-five subjects were included in the study: 27 PRP and 28 SSc, exceeding our sample size calculation. Demographic details of patients are summarised in table 1. Patients with PRP had a significantly lower mean age of onset when compared to SSc (30.3yrs vs. 41.6 yrs, *P*=0.027). The mean age of assessment was also lower for PRP compared with SSc (*P*<0.01). Smoking history and gender did not differ between groups. Medication use at the time of thermographic assessment could not be verified retrospectively and could not be adjusted for in subsequent analysis.

Thermal imaging results

Figure 1 is an example of the typical thermographic appearances obtained at baseline from a patient with RP (secondary to SSc), along with those of a healthy control, demonstrating distal and dorsal regions of interest and the negative DDD characteristic of vascular dysfunction in RP.

Discriminatory capacity of individual digital DDDs at 23℃ baseline

The mean baseline DDD was higher (i.e. warmer) for all digits in the PRP group compared to patients with SSc, although differences between groups only achieved borderline significance owing to the large variation of data and overlap between groups (*P* values 0.06, 0.07 and 0.08 for little, ring and index fingers respectively, table 2). In contrast, no such trend was apparent when comparing the mean DDDs of the thumbs between PRP and SSc (*P*=0.51). A significant difference between PRP and SSc for the proportion of subjects with a DDD<-1°C was identified for the little finger (*P*=0.04), with strong trends for the index and ring fingers (*P*=0.07), whereas there was no apparent difference between groups for the thumbs (*P*=0.33, Table 3).

Comparison between individual digits at baseline

The mean baseline DDD was significantly higher for the thumb when compared with each of the other digits in both PRP and SSc groups (Table 2). Relative sparing of the thumbs was most obvious in SSc (mean difference with thumb ~1.8°C, *P*<0.001 for all comparisons) compared to PRP (mean difference with thumb ~0.9°C, *P*<0.01 for all comparisons, Table 2). Similarly, the proportion of patients with a clinically relevant DDD of <-1°C was generally higher for the fingers compared with the thumbs in both groups although this only achieved statistical significance at baseline for the ring finger in the SSc cohort (50% of thumbs vs. 79% of ring fingers, *P*=0.04, Table 3).

Response to cold stress test

The impact of the cold challenge on the magnitude of the DDD was most pronounced in the PRP group with significant increases in the magnitude of the negative mean DDD gradient for all

digits (mean change ~1.2°C, $P<0.05$, table 2). In contrast, the effect of the cold challenge on the mean DDD in the SSc group was more modest (mean difference ~ 0.5°C) and only achieved statistical significance in the ring and little fingers ($P=0.03$ and $P=0.02$ respectively, table 2). The influence of the cold challenge on the mean DDD was greater for the fingers compared to the thumbs in both groups, accentuating the degree of relative sparing of the thumbs (table 2). Similarly, the proportion of digits with a clinically meaningful DDD (<-1°C) increased following cold challenge in the PRP group for all digits, although the effects were less pronounced than using the mean DDD, only achieving borderline significance ($P=0.05$ for little finger, $P=0.07$ for middle and ring fingers). In contrast, the cold challenge had no effect on the proportion of subjects with a clinically meaningful DDD in the SSc group. The disparity in response to cold challenge between the groups for each endpoint narrowed differences present at baseline, failing to improve, and indeed reducing, the capacity of either endpoint to differentiate between disease states (Tables 2 and 3). We explored the possibility that vascular reactivity (i.e. reversible ischaemia) was significantly greater in PRP compared with SSc and could be used to differentiate between disease groups. We compared the mean change in DDDs for individual digits and composite scores following CST, but differences between PRP and SSc groups failed to achieve statistical significance (data not reported).

Comparison of composite indices of multiple digits and individual digital assessment

The mean maximum DDD across all digits was significantly lower for SSc compared with PRP at baseline (-3.91°C vs. -2.43°C respectively, $P=0.03$). The mean 'worse' DDD of all five digits at baseline was also lower in SSc compared with PRP but the trend failed to reach statistical significance (-2.70°C vs. -1.62°C, $P=0.11$) owing to large variation in the data from each group. Exclusion of the thumbs strengthened the trend moderately (1.79°C vs. 3.02°C, $P=0.07$). Analysis of the proportion of subjects with **any** finger DDD <-1°C at baseline was of also of borderline significance (85.7% vs. 63%, $P=0.05$). As with individual digital analysis, the response of the

composite indices to the CST was greater for PRP compared with SSc groups (Table 2). In light of the disproportionate effect of cold exposure in PRP compared with SSc, the potential of each composite score to differentiate between disease states was lost following cold challenge, as had been demonstrated in individual digit analysis (*P* values between 0.37 and 0.95, Tables 2 and 3). Using the previously proposed cut-off of <-1°C, we evaluated the overall value of identifying any digit with a clinically meaningful DDD of <-1°C for differentiating between patients with SSc from PRP undergoing thermographic assessment (at baseline and following CST). The sensitivity remained high at baseline and following CST (85.7% and 82.1% respectively), at the expense of the specificity, which decreased from 37% at baseline to 18.5% following CST. There were similar reductions in the positive predictive values (PPV, 58.5% to 51.1%) and negative predictive values (NPV, 71.4% to 50%) following CST.

Discussion

The present study is the first to evaluate the influence of the cold challenge on the magnitude of the DDD and it's capacity to differentiate between PRP and SSc. The cold challenge has a disproportionate effect on the DDD in PRP compared with SSc, failing to improve and indeed reducing the discriminatory capacity of the DDD. Lower DDDs at baseline in SSc possibly reflect greater basal vascular resistance and irreversible changes in digital vascular morphology. These differences attenuate the subsequent response to cold exposure. Digital vascular function in PRP meanwhile, is characterised by relatively lower vascular resistance at baseline allowing a more exaggerated vasospastic response to cold exposure, and subsequent greater reduction in the magnitude of the DDD.

Early studies investigating the longitudinal thermal gradient in the thermographic assessment of RP proposed combination of the thermal gradient (similar to the DDD) at baseline with that obtained 10 minutes following cold challenge (Ring, 1980; Ring, 1988). We have demonstrated

that such an approach, whilst potentially improving the discrimination between healthy controls and RP, would be expected to reduce the capacity to distinguish between different RP disease states owing to the disproportionate effect of the cold challenge on the DDD of patients with PRP compared with SSc. The present study questions the value of the CST in the thermographic assessment of RP. Concerns have also been raised regarding the reproducibility of the cold challenge (Bartelink et al., 1993; Cherkas et al., 2003; Herrick and Clark, 1998; O'Reilly et al., 1992). It is important to note that the conditions of the cold stress and thermographic protocol in our study differed slightly in comparison with previous studies evaluating the discriminatory capacity of the DDD (Anderson et al., 2007; Clark et al., 1999). Firstly, the intensity of the cold challenge (20°C) was lower than that used in previously (15°C) however these studies did not specifically investigate the influence of the cold challenge on the discriminatory capacity of the DDD (Anderson et al., 2007; Clark et al., 1999). Secondly, we had insufficient thermographic data following CST to evaluate additional parameters derived from the re-warming curve characteristics investigated previously (e.g. lag time to re-warming, maximum temperature recovery rate and percentage recovery). In the 2 previous studies that have compared the discriminatory capacity of the various re-warming curve characteristics and the DDD baseline, only the maximum temperature recovery rate/gradient matched (but did not improve) the discriminatory capacity of the DDD at 23°C (Anderson et al., 2007; Clark et al., 1999). Removal of the CST from thermographic protocols may facilitate more widespread use of the thermographic assessment of RP, as the time considerations of a well-conducted cold challenge (between 30 and 60 minutes depending on protocol) have restricted greater use of IRT outside that of specialist centres.

Evaluation of the discriminatory capacity of the DDD at 23°C baseline was not the main purpose of this study. Nonetheless, our findings contrast with recent reports attaching prognostic importance with involvement of the thumbs (Chikura et al., 2010). We did identify evidence of

thermographic sparing of the thumbs in RP as previously reported (Chikura et al., 2010; Chikura et al., 2008), however the magnitude of the mean DDD, and proportion of patients with a DDD of the <-1°C of the thumbs did not aid differentiation between disease states and possibly lacked the discriminatory potential of the DDD in the fingers. Moreover, in contrast to the findings of Chikura *et al*., we could not easily differentiate between PRP and SSc using individual digits for the mean DDD at baseline (Chikura et al., 2010). Large variation in DDDs within each group (SD up to 3.1) was the principle factor precluding differentiation between disease states highlighting a major limitation of use of IRT in disease classification. Significant differences between PRP and SSc were identified for age of RP onset, the maximum DDD across all digits and for the proportion of patients with a DDD <1°C for the little finger. An obvious explanation for the lack of agreement was the smaller study size compared with some previous studies (Anderson et al., 2007; Chikura et al., 2010). Nonetheless, our study was of comparable size to previous studies evaluating the DDD (Chikura et al., 2008; Clark et al., 1999) and sufficiently powered to detect a difference of > 1SD between groups. Differences in patient characteristics may have also contributed to disparity between our findings and previous work. The mean DDDs at baseline within our PRP group were lower than previously reported (Anderson et al., 2007; Chikura et al., 2010; Chikura et al., 2008; Clark et al., 1999) suggesting greater vascular dysfunction within our population of unselected patients with PRP referred for thermographic assessment. This may reflect a higher threshold for referral from primary care locally. A population-based study may allow easier differentiation between groups owing to the inclusion of a greater proportion of patients with mild RP, insufficient to warrant secondary care referral. It is possible that use of vasoactive medications differed between the 2 groups, which may have influenced peripheral vascular responses to cold challenge. Unfortunately, the retrospective nature of the study precluded comprehensive assessment of medication usage, which had not been routinely documented on the day of thermographic assessment.

This is the first study to compare the various reported methods for analysing the DDD, such as individual digital assessment versus composite indices of multiple digits. Our findings would generally support the use of composite indices of the four fingers (excluding the thumbs) when attempting to differentiate between disease states. Furthermore, the mean maximum DDD across all digits and the number of patients with any finger DDD of <1°C utilised in early studies of the DDD (Anderson et al., 2007; Clark et al., 1999) appears to provide greater discriminatory capacity than DDD indices derived by first calculating the lower score from each pair of digits prior to further analysis that has been adopted in more recent studies investigating the DDD (Chikura et al., 2010; Chikura et al., 2008). The sensitivity for the number of patients with any digit <-1°C at 23°C in our study (85.7%) was greater than that reported at 30°C in previous work (69%, Anderson et al., 2007), however this improved sensitivity has predictable negative effects on the specificity, PPV and NPV which all benefit from increasing room temperature to 30°C to promote vasodilatation prior to undertaking assessment of the DDD (Anderson et al., 2007).

Conclusions

We have demonstrated that the cold challenge does not improve the discriminatory capacity of the thermographic DDD in differentiating between disease states in the diagnostic assessment of RP. We do not currently propose removal of the cold challenge from the thermographic assessment of RP, but have highlighted potential limitations in its clinical application and the need for additional work to re-establish its role. Further work investigating thermographic parameters such as the DDD, and the contribution of the CST, is required to identify applications beyond that of disease classification which might include; quantification of disease activity and responsiveness to therapeutic intervention, correlates with pain, disability and quality of life, in addition to the prognostic potential in SSc in identifying patients at risk of future digital ischaemic complications.

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Conflicts of interest

The authors have declared no conflicts of interest.

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Figures and Tables

Figure 1. Typical thermographic images of the hands at baseline (23°C) of: A) Dorsal aspect of hands of a patient with systemic sclerosis. Note the asymmetry, relative thumb sparing and significant negative DDD affecting several digits. The distal and dorsal regions of interest are highlighted on the right hand. B) Dorsum of right hand and palmer aspect of left hand of a healthy control demonstrating symmetrical perfusion and a positive DDD reflecting normal digital vascular perfusion at the fingertips. The colour chart provides a temperature scale.

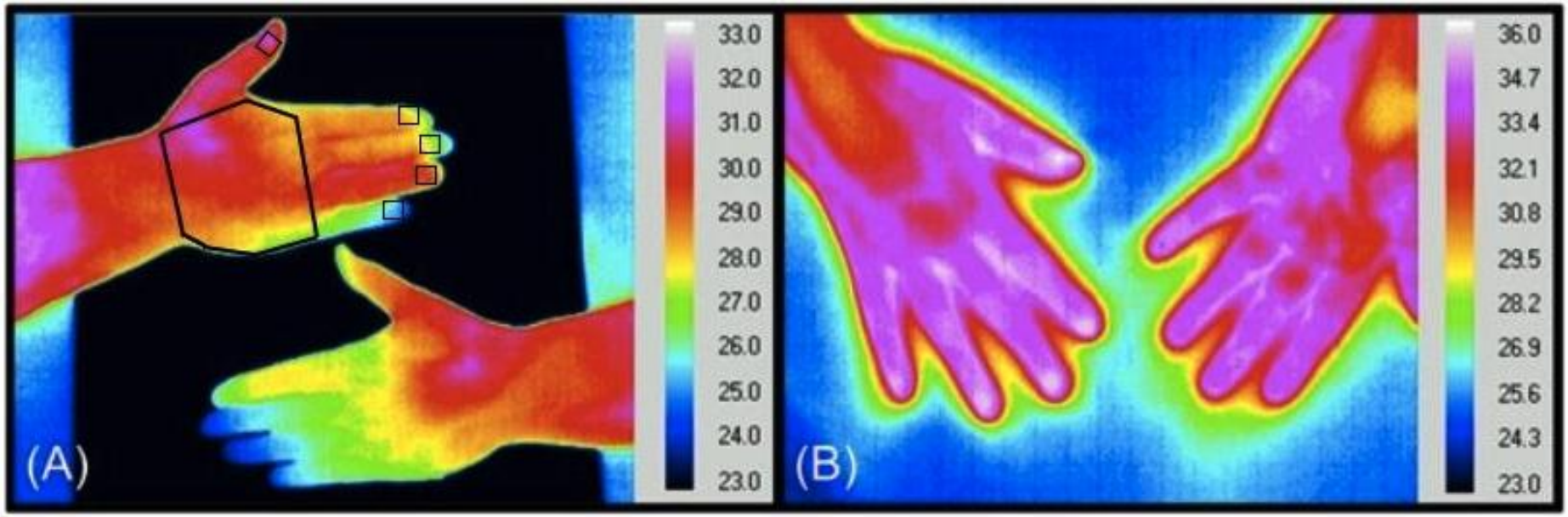

Table 1. Patient demographics. Data presented as n (%) unless stated. PRP, primary Raynaud's phenomenon; SSc, systemic sclerosis; NS, non-siginificant; lcSSc, limited cutaneous SSc; dcSSc, diffuse cutaneous SSc; ACA, anticentromere antibody; Topo-1, anti-topoisomeras-1.

	PRP (n = 27)	SSc (n = 28)	PRP vs. SSc *P* value
Age at assessment, yrs (SD)	43.15 (17.3)	54.9 (13.5)	0.007
Age at RP onset yrs, (SD)	30.3 (18)	41.6 (16.7)	0.027
Gender, male:female	6:21	7:21	NS
Smoking			
Current	4(14.8)	4 (14.3)	NS
Previous	3 (11.1)	5 (17.9)	NS
Never	18 (66.7)	16 (57.1)	NS
Not recorded	2 (7.4)	3 (10.7)	NS
Underlying diagnosis			
lcSSc	-	21 (75)	
dcSSc	-	7 (25)	
Antibody			
ACA	-	19 (67.8)	
Anti-topo-1	-	5 (17.8)	
Anti-Ro/La	-	3 (10.7)	
Anti-U3-RNP	-	1 (3.6)	
Anti-Th	-	2 (7.1)	

Table 2. Mean 'distal-dorsal difference' (DDD) for individual digits (calculated using the 'worse' i.e. lower DDD from each pair of digits [right or left hand]) and composite scores for each group at 23°C baseline and 10 minutes post standardised cold challenge. All values expressed in °C as Mean (SD) unless stated

PRP, primary Raynaud's phenomenon; SSc, systemic sclerosis; CST, cold stress test

† *P*<0.05 vs. thumb; †† *P*<0.005 vs. thumb for corresponding assessment;

*** *P*<0.05, ***P*<0.01, baseline vs. post CST**

		PRP (n=27)	SSc (n=28)	PRP vs. SSc, *P* value
Individual digits				
Thumb	23°C baseline	-0.97 (2.6)	-1.42 (2.5)	0.51
	Post CST	-1.72 (2.0) *	-1.78 (3.1)	0.95
Index	23°C baseline	-1.44 (2.7) †	-2.72 (2.6) ††	0.08
	Post CST	-2.72 (3.1) † **	-3.22 (3.1) ††	0.55
Middle	23°C baseline	-1.91 (2.7) ††	-2.88 (2.5) ††	0.18
	Post CST	-3.07 (2.9) †† *	-3.42 (3.0) ††	0.67
Ring	23°C baseline	-1.92 (2.7) ††	-3.21 (2.4) ††	0.07
	Post CST	-3.21 (3.1) †† *	-3.98 (2.8) †† *	0.34
Little	23°C baseline	-1.86 (2.7) †	-3.24 (2.6) ††	0.06
	Post CST	-3.30 (3.0) †† *	-4.00 (3.0) †† *	0.39
Composite indices				
Maximum DDD (across all digits)	23°C baseline	-2.43 (2.5)	-3.91 (2.5)	0.03
	Post CST	-3.75 (2.8) *	-4.41 (2.7)	0.37
Mean 'worse' DDD for all digits	23°C baseline	-1.62 (2.6)	-2.70 (2.2)	0.11
	Post CST	-2.81 (2.9) **	-3.28 (2.8) *	0.54
Mean 'worse' DDD for fingers (minus thumbs)	23°C baseline	-1.79 (2.6)	-3.02 (2.3)	0.07
	Post CST	-3.08 (3.0) *	-3.66 (2.8) *	0.46

Table 3. Proportion of patients with a clinically relevant DDD of <-1°C for individual digits, and any digit, at 23°C and 10 minutes post standardised cold challenge with comparison between primary RP and SSc. All data expressed as n (%) unless stated.

PRP, primary Raynaud's phenomenon; SSc, systemic sclerosis; CST, cold stress test

† ***P*<0.05 vs. thumb for corresponding assessment**

		PRP (n=27)	SSc (n=28)	PRP vs. SSc *P* value
Individual digits				
Thumb	23°C baseline	10 (37)	14 (50)	0.33
	Post CST	14 (62)	15 (54)	0.9
Index	23°C baseline	14 (52)	21 (75)	0.07
	Post CST	18 (67)	20 (71)	0.7
Middle	23°C baseline	15 (56)	19 (68)	0.35
	Post CST	21 (78) †	20 (71)	0.29
Ring	23°C baseline	15 (56)	22 (79) †	0.07
	Post CST	21 (78) †	22 (79) †	0.94
Little	23°C baseline	13 (48)	21 (75)	0.04
	Post CST	20 (74)	21 (75)	0.94
Composite indices				
Any digit DDD <-1°C	23°C baseline	17 (63)	24 (86)	0.05
	Post CST	22 (82)	23 (82)	0.95